BOX PCT

ATTORNEY'S DOCKET NO: 24390

U.S. DEPARTMENT OF COMMERCE, PATENT AND TRADEMARK OFFICE		DATE: 29 September 2000 (29.09.2000)
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U.S. APPLN. NO. (if known): Not Yet Assigned 09/647457
INTERNATIONAL APPLICATION NO.: PCT/IL99/00190	INTERNATIONAL FILING DATE: 30 March 1999 (30.03.99)	PRIORITY DATE CLAIMED: 02 April 1998 (02.04.98)

TITLE OF INVENTION: **ASSAY FOR THE DIAGNOSIS OF SCHIZOPHRENIA BASED ON A NEW PEPTIDE**

APPLICANT(S) FOR DO/EO/US: SHINITZKY, Meir; DECKMANN, Michael

Applicant hereby submits to the Unites States Designated/Elected Office (DO/EO/US) the following items and other information:

1. X This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.

2. __ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.

3. X This express request to begin national examination procedures (35 USC 371(f)) at any time rather than delay examination until the expiration of the time limit set in 35 USC 371(b) and PCT Articles 22 and 39(1).

4. X A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. x A copy of the International Application as filed (35 U.S.C. 371(c)(2)):

   a. X is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ___ has been transmitted by the International Bureau.
   c. ___ is not required, as the application was filed in the United States Receiving Office (RO/US)

6. __ A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. X Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))

   a. __ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. __ have been transmitted by the International Bureau.
   c. __ have not been made; however, the time limit for making such amendments has NOT expired.
   d. X have not been made and will not be made.

8. __ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).

9. __ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).

10. __ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

ITEMS 11. TO 16. BELOW CONCERN OTHER DOCUMENT(S) OR INFORMATION INCLUDED:

11. __ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12. __ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. X A **FIRST** preliminary amendment.
    _ A **SECOND** or **SUBSEQUENT** preliminary amendment

14. __ A substitute specification.

15. __ A change of power of attorney and/or address letter.

16. X TRANSMITTAL FORM; FEE CALCULATION; INTERNATIONAL PUBLICATION WO 99/51725; INTERNATIONAL PUBLICATION DATE 14 OCTOBER 1999; APPLICATION CONSISTING OF 36 PAGES INCLUDING; 20 PAGES TEXTUAL SPECIFICATION, 4 PAGES OF 14 CLAIMS; 1 COVER PAGE CONTAINING THE ABSTRACT; 4 SHEETS DRAWINGS; 7 PAGES SEQUENCE LISTING; PRELIMINARY AMENDMENT; UNEXECUTED INVENTOR'S DECLARATION; PCT/ISA/220 NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT; PCT/ISA/210 INTERNATIONAL SEARCH REPORT; PCT/IPEA/408 WRITTEN OPINION; PCT/IPEA/416 NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT; PCT/IPEA/409 INTERNATIONAL PRELIMINARY EXAMINATION REPORT.

ATTORNEY'S DOCKET NO: 24390

U.S. APPLICATION NO. Not yet assigned 09/647457	INTERNATIONAL APPLICATION NO. PCT/IL99/00190	DATE: 29 September 2000 (29.09.2000)

17. x The following fees are submitted:	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5): Search Report has been prepared by the EPO or JPO:.....$840.00	$ 840.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482).....$670.00		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)).....$760.00		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....$970.00		
International preliminary examination fee (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4).....$ 96.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	**$ 840.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than ___ 20 ___ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NO. FILED	NO. EXTRA	RATE		
TOTAL	13 -20=	0	X $ 18.00	$ **0.00**	
INDEPENDENT	4 - 3=	1	X $ 78.00	$ 78.00	
Multiple dependent claims(s) (if applicable)			+ $260.00	$ 0.00	
TOTAL OF ABOVE CALCULATIONS =				$ **918.00**	
Reduction by ½ for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				$ **0.00**	
SUBTOTAL =				$ 918.00	
Processing fee of **$130.00** for furnishing the English translation later than ___ 20 ___ 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$ 0.00	
TOTAL NATIONAL FEE =				$ 918.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00 per property +**				$ **0.00**	
TOTAL FEES ENCLOSED =				$ **918.00**	
				Amount to be: refunded	$
				charged	$

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U.S. APPLICATION NO. Not yet assigned 09/647457	INTERNATIONAL APPLICATION NO. PCT/IL99/00190	DATE: 29 September 2000 (29.09.2000)

a. X One check in the amount of $918.00 to cover the above fee is enclosed.

b. ___ Please charge my Deposit Account No. 14-0112 in the amount of $_____ to cover the above fees. (A duplicate copy of this sheet is enclosed.)

c. X The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0112.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed to request that the application be restored to pending status.

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Rev. 02/98

BOX PCT

Attorney Docket No. 24390

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
SHINITZKY, Meir; DECKMANN, Michael
International Application No PCT/IL99/00190
Serial No.
International filing date: 30 March 1999 (30.03.99)
Filed: September 29, 2000
For: **ASSAY FOR THE DIAGNOSIS OF SCHIZOPHRENIA BASED ON A NEW PEPTIDE**

PRELIMINARY AMENDMENT

The Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Before calculating the filing fee for the above identified application, please enter the following amendments:

IN THE CLAIMS:

Claim 3, line 1, delete "or 2"

Claim 4, line 1, delete "any one of claims 1-3" and insert in lieu thereof --claim 1--

Claim 5, line 1, delete "any one of claims 1-4" and insert lieu thereof --claim 1--

Claim 6, line 1, delete "any one of claims 1-4" and insert in lieu thereof --claim 1--

Claim 13, line 1, delete "any of Claims 8-12" and insert in lieu thereof --claim 8--

8. (amended) An assay for the diagnosis of schizophrenia in an individual, comprising the following steps:

(a) obtaining a sample from said individual being a blood sample, a platelet-containing fraction thereof, or a fraction containing platelet-associated antibodies(PAA) shed from the platelets;

(b) contacting said sample with a peptide [capable of binding to antibodies that are found in elevated levels in body fluids of schizophrenic patients.] having the amino acid sequence of Seq.ID.No.2;

(c) determining the level of binding of said peptide to said sample, a level higher than the binding level of said peptide to a sample from non-schizophrenic individuals indicating that said individual has a high likelihood of having schizophrenia.

Cancel claim 9.

14.(amended) A kit for use in the diagnosis of schizophrenia comprising:

i. a support comprising one or more peptides in accordance with [any one of claims 1-7] claim 1 immobilized onto it;

ii. an anti-human immunoglobulin antibody or fragment thereof which maintains the binding characteristics of the whole antibody; said antibody or fragment thereof conjugated to a detectable marker;

iii. reagents required for carrying out the assay, and;

iv. instructions for use.

REMARKS

The above amendments have been made to remove multiple dependencies from the claims, and no new matter has been added.

Respectfully submitted,

NATH & ASSOCIATES PLLC

By: _____

Gary M. Nath
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Date: September 29, 20000
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4/pts.

ASSAY FOR THE DIAGNOSIS OF SCHIZOPHRENIA BASED ON A NEW PEPTIDE

FIELD OF THE INVENTION

The present invention is generally in the field of assays for the diagnosis of mental disorders. More specifically, the present invention provides an assay for the diagnosis of schizophrenia.

PRIOR ART

The following is a list of prior art publications referred to in the present specification.

1. Carpenter, W.T., and Buchanan, R.W., *Review, N. Engl. J. Med.*, **330**681-690, 1994.

2. Knight, J.G., *Find. Exp. Clin. Pharmacol.*, **6**:395-408, 1984.

3. De Lisi, L.E., and Crow, T.J., *Psychiatr. Clin. North Am.*, **9**:115-132, 1987.

4. Ganguli, R., Rabin, B.S., Kelly, R.H., Lyte, M. and Ragu, U., *Ann. N.Y. Acad. Sci.*, **496**:676-690, 1987.

5. Shinitzky, M., Deckmann, M., Kessler, A., Sirota, P., Rabbs, A. and Elizur, A., *An. N.Y. Acad. Sci.*, **621**:205-217, 1991.

6. Deckmann, M., Shinitzky, M., Leykin, I., Cheng, D., Guy, J., Avnon, M., Salganik, I., Amiri, Z., Schlossberg, A., Leibu, E., and Rafael, C., *The Italian J. Psychiatr. Behav. Sci.*, **6**:29-34, 1996.

7. PCT Patent Application Publication Number WO 95/23970.

The acknowledgement herein of the above art should not be construed as an indication that this art is in any way relevant to the patentability of the invention as defined in the appended claims.

The above publications will be acknowledged in the following by indicating their number from the above list.

BACKGROUND OF THE INVENTION

Schizophrenia is a syndrome which encompasses a variety of mental symptoms like auditory hallucinations, paranoia, delusions, catatonia, bizarre behavior or emotional withdrawal. Schizophrenia affects about 1% of the total population and its economical as well as social burden on society are enormous. The onset of the disease occurs at an early age and thus patients typically need life-long medical and psychiatric supervision. Schizophrenia is, therefore, rated as one of the most costly diseases in the industrial world[1].

There are various known risk factors associated with schizophrenia such as genetic predisposition, birth during winter and complications during pregnancy and birth. Viral infections and subsequent autoimmune reactions have also been proposed as possible causative factors[2-4]. The involvement of autoantibodies against platelets in schizophrenic patients was also shown as elevated levels of autoantibodies were detected in schizophrenic and demented patients as compared to control subjects, bipolar, depressed, personality disordered or schizoeffective patients[5-6]. Western Blot analysis revealed a pattern of platelet antigens recognized by autoantibodies obtained from schizophrenic patients which differed from that recognized by autoantibodies obtained from patients suffering from autoimmune thrombocytopenia and dementia[7]. The antigen bound specifically by autoantibodies obtained from schizophrenic patients has been characterized by its molecular weight.

SUMMARY OF THE INVENTION

In accordance with the invention, several proteins which bind autoantibodies that are found in elevated levels in body fluids of schizophrenic patients have been identified. The antibodies which these proteins bind are typically platelet associated autoantibodies (PAA). Such autoantibodies obtained from schizophrenic patients (hereinafter "*schizophrenic derived antibodies – SDA*") were shown to bind the above antigens while autoantibodies obtained from control non-schizophrenic individuals (hereinafter "*non-schizophrenic derived antibodies - NSDA*") did not.

The proteins which were shown to be capable of binding SDA were identified and further characterized by chemical and enzymatic methods. Some of the identified immuno-reactive proteins are known proteins such as glyceraldehyde-3-phosphate dehydrogenase (G3PD), enolase, keratin, hepatocyte growth factor, extracellular calcium sensing receptor and several more. By digesting the rabbit protein enolase, an immunologically active peptide was revealed which had a high binding activity to SDAs.

The revealed peptide, being the immunologically active epitope of the enolase protein, comprised twenty eight amino acids of the following sequence:

SGETEDTFIADLVVGLCTGQIKTGAPCR (Seq. ID No. 1)

On the basis of the revealed peptide, additional peptides were synthesized and highly active ones (i.e. such which had a high binding activity to SDAs as compared to a very low binding activity to NSDA or which do not bind NSDA at all) were identified. Moreover, the synthesized active peptides were capable of differentiating for the first time between plasma samples obtained from schizophrenic patients and plasma samples obtained from control non-schizophrenic individuals.

Further analysis of one of the synthesized highly active peptides (Seq. ID No. 2) showed that this peptide forms a ring via two cysteins and a

dimer via the remaining free cystein. The peptide in this form is most active in its ability to bind SDA.

As described below, the antigenic epitope of the synthetic highly active peptides of the invention seems to be a three dimensional spatial eptiope.

The present invention thus provides a peptide which binds antibodies that are found in elevated levels in body fluids of schizophrenic patients.

The invention further provides a peptide capable of binding antibodies that are found in elevated levels in body fluids of schizophrenic patients, wherein the peptide binds antibodies that are capable of specific binding to a peptide having the following amino acid sequence: LVVGLCTCQIKTGPAC (I.D. No. 2). Several non-limiting examples of such peptides are the following:

iii. IADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 3)

iv. ADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 4)

v. DLVVGLCTGQIKTGAPCR (Seq. I.D. No. 5)

vi. LVVGLCTGQIKTGAPCR (Seq. I.D. No. 6)

vii. LVVGLCTGQIKTGPACR (Seq. I.D. No. 7)

viii. LVVGLCTPQIKTGPACR (Seq. I.D. No. 8)

The invention also provides a peptide which is capable of binding antibodies that are found in elevated levels in body fluids of schizophrenic patients, such peptides capable of binding antibodies which do not bind to peptides selected from the group consisting of :

i. SGETEDTFIADLVVGLCTGQ (Seq. I.D. No. 9)

ii. VVGLCTGQIKTGAPCR (Seq. I.D. No. 10)

iii. CTGQIKTGAPCR (Seq. I.D. No. 11)

iv. LVVGLCTGQIKTGAPC (Seq. ID. No. 12)

v. LVVGLCTGQIKTGAP (Seq. ID No. 13)

vi. LVVGLCTGQIKTGPAC (Seq. ID No. 14)

The invention also provides a peptide capable of binding to antibodies that are found in elevated levels in body fluids of schizophrenic patients comprising an amino acid sequence selected from the group, consisting of:

i. SGETEDTFIADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 1)
ii. LVVGLCTCQIKTGPAC (Seq. I.D. No. 2)
iii. IADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 3)
iv. ADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 4)
v. DLVVGLCTGQIKTGAPCR (Seq. I.D. No. 5)
vi. LVVGLCTGQIKTGAPCR (Seq. I.D. No. 6)
vii. LVVGLCTGQIKTGPACR (Seq. I.D. No. 7)
viii. LVVGLCTPQIKTGPACR (Seq. I.D. No. 8)

By a preferred embodiment the invention provides a peptide capable of binding antibodies that are found in elevated levels in body fluids of schizophrenic patients selected from the group consisting of:

i. SGETEDTFIADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 1)
ii. LVVGLCTCQIKTGPAC (Seq. I.D. No. 2)
iii. IADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 3)
iv. ADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 4)
v. DLVVGLCTGQIKTGAPCR (Seq. I.D. No. 5)
vi. LVVGLCTGQIKTGAPCR (Seq. I.D. No. 6)
vii. LVVGLCTGQIKTGPACR (Seq. I.D. No. 7)
viii. LVVGLCTPQIKTGPACR (Seq. I.D. No. 8)

The letters used above (and hereinafter) to denote specific a.a. are in accordance with the one-letter amino acid (a.a.) symbols recommended by the IUPAC-IUB Biochemical Nomenclature Commission.

Without being bound by theory, on the basis of the results obtained in accordance with the invention, it has become clear that the structure of the antigenic epitope of the peptides to which SDAs are capable of binding at a substantially higher degree as compared to NSDAs is a

three-dimensional epitope. By using a computerized program based on minimal energy calculations, the antigenic epitope of a peptide in accordance with the invention is predicted as being a cyclic structure comprising a hydrophobic core and an extension having about two positive charges. The positive charged extensions may be positioned in one of many possible spatial orientations.

The binding activity of the peptide of the invention to various antibodies may be determined by any of the methods known *per se* such as ELISA or Western Blotting. For example, a tested peptide may be analyzed for its binding activity to antibodies by subjecting it to polyacrylamide gel electrophoresis, blotting it onto PVDS membranes which are then reacted with SDA and compared to their reaction with NSDA.

The extent of binding of the peptides of the invention to PAA can be determined by using any detection system known in the art such as antibodies against human immunoglobulin or fragments thereof linked to a detectable marker. The marker may be a radioactive group, a fluorescent group, an enzyme capable of catalyzing a reaction yielding a detectable product, a biotin group capable of being detected by avidin, etc.

By a preferred embodiment of this aspect, the peptides of the invention are bound onto a solid support such as e.g. a PVDF membrane, reacted with the tested sample and the level of binding of the PAAs in the sample is determined using an anti-human Fc antibody conjugated to a detectable marker.

In accordance with a particular embodiment, the determination of the level of autoantibodies bound to a tested peptide is determined by using anti-human Fc conjugated to horseradish peroxidase (SIGMA) and Fast-DAB™ (SIGMA) or 4-Chloro-naphthol (SIGMA) as the color reagent.

In order for the binding of the tested peptide in accordance with the invention to SDA to be considered *"substantially higher"* than its binding to NSDA. the level of binding to SDA should be statistically significantly

higher than its binding to NSDA as determined by any of the statistical methods known in the art (e.g. Students' t-Test) which are used in connection with results obtained by the experimental methods mentioned above.

Analogs of all the above peptides also form an aspect of the present invention. As will be appreciated by any person versed in the art, the amino acid sequence of the peptides of the invention may be altered, for example by addition, replacement or deletion of one or more amino acids without substantially altering the binding capacity of the peptide to SDAs. Thus for example the leucine positioned in the first position of the amino acid sequence of a peptide of the invention may be substituted by the amino acid glycine or valine which belong to the same family of amino acids without altering the binding activity of the peptide. A person versed in the art will have no difficulty in determining by which amino acid each of the amino acids of the peptide may be replaced in accordance with the known grouping of amino acids into families as may be found, for example, in Molecular Biology of the Cell Editors Alberts B. *et al.*, Garland Publishing, Inc., New York and London, 2nd Edition, 1989, pages 54-55.

Analogs which fall under the scope of the peptides of the present invention are such which have substantially the same level of binding activity to SDAs, as the peptides i.e. have a higher level of binding to SDAs as compared to NSDAs as determined by any of the methods known in the art such as for example that described in Example 1 below.

The peptide of the invention may be obtained by enzymatic digestion (e.g. using Clostrapain) or chemical (CNBr) digestion of a longer protein. In such a case, the resulting peptides are separated by methods known in the art such as by RP-HPLC and the separate peptides may then be used for sequencing (e.g. by Eurosequence b.v. (Nijenborgh 4; 9749 Gronigen; The Netherlands)) and analyzed for their binding capability to SDAs as described above.

Peptides in accordance with the invention may also be synthesized by methods known in the art such as on Abimed 522 at a 10 μmol scale by Eurosequence b.v. (see detailed explanation in the examples below). The binding activity of the newly synthesized peptides will be determined using any of the assays mentioned above.

The peptides of the invention are capable of differentiating between a sample obtained from an individual suffering from schizophrenia and a sample obtained from a non-schizophrenic individual and are therefore useful in the diagnosis of schizophrenia in an individual. Thus, by another of its aspects, the present invention provides a peptide for use in the diagnosis of schizophrenia in an individual, said peptide capable of binding antibodies that are found in elevated levels in body fluids of schizophrenic patients.

The sample of the individual to be tested is typically a PAA containing fraction of a blood sample comprising platelets. However, in accordance with the present invention it has become possible for the first time to determine the probability of existence of schizophrenia in a plasma sample taken from tested individuals without the need to first isolate PAA from the sample. Thus, in accordance with the invention, the sample of an individual to be tested may either be a plasma sample or a PAA containing fraction obtained therefrom by any of the methods known in the art (e.g. by obtaining a platelet-rich plasma (PRP) and isolating PAA therefrom).

Since the peptides of the invention are capable of binding to a different extent to platelet derived autoantibodies in a sample obtained from a schizophrenic patient as compared to a sample obtained from a control non-schizophrenic individual, the peptides may be used in an assay for diagnosis of schizophrenia in an individual. Therefore, the present invention by an additional aspect provides an assay for the diagnosis of schizophrenia in an individual, comprising the following steps:

(a) obtaining a sample from said individual being a blood sample, a platelet-containing fraction thereof, or a fraction containing platelet-associated antibodies (PAA) shed from the platelets;

(b) contacting said sample with a peptide capable of binding to antibodies that are found in elevated levels in body fluids of schizophrenic patients.

(c) determining the level of binding of said peptide to said sample, a level higher than the binding level of said peptide to a sample from non-schizophrenic individuals indicating that said individual has a high likelihood of having schizophrenia.

By a further embodiment the peptide of step (b) above is a peptide which binds antibodies that are capable of specific binding to a peptide having the amino acid sequence of Seq. ID. No. 2. By another embodiment the peptide in step (b) above comprises an a.a. sequence selected from the group consisting of:

i. SGETEDTFIADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 1)
i. LVVGLCTCQIKTGPAC (Seq. I.D. No. 2)
iii. IADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 3)
iv. ADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 4)
v. DLVVGLCTGQIKTGAPCR (Seq. I.D. No. 5)
vi. LVVGLCTGQIKTGAPCR (Seq. I.D. No. 6)
vii. LVVGLCTGQIKTGPACR (Seq. I.D. No. 7)
viii. LVVGLCTPQIKTGPACR (Seq. I.D. No. 8)

By a preferred embodiment, the peptide in step (b) is a peptide selected from the group consisting of:

i. SGETEDTFIADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 1)
ii. LVVGLCTCQIKTGPAC (Seq. I.D. No. 2)
iii. IADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 3)
iv. ADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 4)
v. DLVVGLCTGQIKTGAPCR (Seq. I.D. No. 5)

vi. LVVGLCTGQIKTGAPCR (Seq. I.D. No. 6)

vii. LVVGLCTGQIKTGPACR (Seq. I.D. No. 7)

The present invention also provides a kit useful in the above assay. The kit of the invention comprises a support comprising one or more peptides of the invention immobilized onto it and an anti-human immunoglobulin antibody or fragment thereof. The anti-HIG antibody may be conjugated to a detectable marker or alternatively, the kit may also comprise a second type of antibodies directed against said first antibodies, wherein the second antibodies are conjugated to a detectable marker. The kit will also comprise various reagents required for carrying out the assay as well as instructions for use.

The invention will now be illustrated in the following non-limiting description of specific embodiments and accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a graphical representation showing binding activity of the Peptide 14 having Seq. I.D. No. 2 to PAAs prepared from samples obtained from schizophrenic patients (Fig. 1A) and non-schizophrenic individuals (Fig. 1B). The peptide having Seq. I.D. No. 9 was used as a negative control.

Fig. 2 is a graphical representation showing binding activity of peptide 14 (Seq. I.D. No. 2) to plasma samples obtained from schizophrenic patients (Fig. 2A) and non- schizophrenic individuals (Fig. 2B). The peptide having Seq. I.D. No. 9 was used as a negative control.

Fig. 3 is a graphical representation showing a schematically predicted three-dimensional structure of the antigenic epitope of the peptides of the invention as determined by a computerized program based on minimal energy calculations.

Fig. 4 is an x-ray of a three-dimensional structure of enolase generated from a public peptide database and compared with the water model of the peptides of the invention.

The amino acids found to exist in the epitope are marked as follows:

L = leucine

A = alanine

P = proline

R = arginine

K = hystidine

EXAMPLES

Materials and Methods

1. Platelets and anti-platelet autoantibodies

Venous blood (20 ml) was drawn with heparin as anticoagulant from patients and control subjects. Platelet rich plasma (PRP) was obtained by centrifugation (100 g for 20 mins) at room temperature. Plasma free platelets were obtained by washing them three times with phosphate buffered saline (PBS) supplemented with 10 ml mM EDTA as anticoagulant (4000 g; 15 mins; 4°C). For the isolation of anti-platelet antibodies, the platelets were incubated with 0.1 M glycine/10 mM EDTA, pH 2.8, for 10 min. at room temperature and then centrifuged (4000 g; 15 min; 4°C). The supernatant containing the anti-platelet antibodies, was neutralized with saturated Na_2PO_4 solution and stored at -20 until use.

2. Preparative isoelectric focusing

Platelet concentrates of blood group 0 were purchased from a local blood bank and washed three to five times with PBS/10 mM EDTA (4000 g; 15 min; 4°C) until the supernatant was free of plasma. The platelets (about 20 concentrates) were first solubilized with 20 ml 0.5% Triton X-100/0.5%

NP40 in water for 15 min. at room temperature under gentle shaking. The suspension was centrifuged (10000 g, 15 min. 4°C), the supernatant removed and the pellet two more times extracted with 0.1% Triton X-100 in water. The three supernatants were combined and Ampholyte™ 3/10 (BioRad) was added to a final concentration of 1%. This solution was loaded into the ROTOFOR™ chamber (capacity 60 ml) and the preparative isoelectric focusing was then performed according to the instruction manual of the manufacturer (BioRad). Typically, the focusing was finished after 4.5 h (10°C; 10 Watt constant power). Twenty fractions were harvested and the pH of the fractions determined (pH gradient 1.5-12). The fractions were stored at -20°C until further use.

3. Identification of immuno-reactive fractions

The fractions were analyzed for immuno-reactivity by polyacrylamide (10%) gel electrophoresis, blotting the proteins onto PVDF membranes and probing the membrane with 1 ml auto-antibodies in 50 ml incubation buffer. Anti-human Fc conjugated to horseradish peroxidase (goat) from SIGMA (1:500 dilution) and Fast-DAB™ (SIGMA) or 4-Chloro-naphthol (SIGMA) were used as color reagent in order to detect bound human anti-platelet antibodies. Immuno-reactivity was observed in the fractions with a pH ranging from 6.0 to 10.0.

4. Preparative polyacrylamide (8%) gel electrophoresis

The immuno-reactive fractions (pH 6-10) were combined and separated according to molecular weight under reducing conditions by preparative SDS polyacrylamide gel (8% and 8 cm height) in a PrepCell from BioRad according to the instruction manual of the manufacturer. Fractions (n=400) of 1.5 ml were collected: every tenth fraction was analyzed by SDS

gel electrophoresis followed by silver staining to determine the molecular weight distribution in the 400 fractions.

5. Identification of immuno-reactive fractions

Every fifth fraction (0.1 ml) was dot blotted onto PVDF membranes using the DotBlot device (96 wells) from BioRad. Immuno-reactive fractions were then detected as described above (1.3)

6. Identification of immuno-reactive proteins

As described previously, a variety of immuno-reactive proteins were identified. Priority for sequencing was given to proteins with a high ratio of reactivity to protein amount. Preparation of sample was typically done in the following way: The fractions (+/- 10) around a positive fraction were re-analyzed as described above under 1.5. The positive fractions were combined, lyophilized, re-separated on an analytical (0.75 mm) SDS polyacrylamide (10%) gel and stained with Coomassie Blue. The band was excised and sent to Eurosequence b.v. (enzymatic digestion, RP-HPLC separation of peptides followed by amino acid sequencing).

7. Identification of immuno-reactive epitope

Of the identified proteins, two were found to be commercially available:

a) Glyceraldehyde-6-phosphate dehydrogenase (G6PD)

b) Enolase

About 10 mg protein was digested either enzymatically (Clostrapain) or chemically (CNBr) and the resulting peptides were separated by RP-HPLC. Aliquot (20%) of all fractions were sent by Eurosequence b.v. to the Main Inventor for analysis of immuno-reactivity as described under 1.5. Only the enzymatic digest of the Enolase resulted in an active fragment which was subsequently sequenced by Eurosequence b.v.

8. Peptide synthesis

Various peptides were synthesized on Abimed 522 at a 10 micromol scale by Eurosequence b.v. Peptides were routinely dissolved in 1 ml water/DMF/DMSO (1:1:1;v/v/v). Peptides were line-blotted onto PVDF membranes and tested for immuno-reactivity as described above.

9. Epitope scanning

Water models of the peptides of the invention were calculated on a MacIntosh computer system. An x-ray three dimensional structure of enolase was generated from a public peptide database and the surface of the enolase was scanned to find epitopes which match the epitopes of the peptides calculated by the water model.

EXAMPLE 1: Identification of immuno-reactive proteins

The following proteins have been identified as such capable of binding autoantibodies present in high levels in schizophrenic patients at a high level as determined by the assay described in 1.3 above:

Protein:

Glyceraldehyde-6-phosphate dehydrogenase
Enolase
Keratin
Hepatocyte growth factor
Extracellular calcium sensing receptor

The above identified proteins were tested for their binding capability to plasma samples obtained from schizophrenic patients and to plasma samples obtained from control non-schizophrenic patients. The results showed that it was not possible to use the above proteins to discriminate between a plasma sample obtained from a schizophrenic patient and that

obtained from a non-schizophrenic individual, i.e. the binding results were not conclusive.

The binding activity of the above two enzymes was then tested by reacting them with SDAs (prepared from samples obtained from schizophrenic patients) and to NSDA (prepared from control non-schizophrenic individuals). As seen in Table 1 below, in this case binding of the proteins to SDAs was substantially higher than their binding to NSDAs expressed by the number of samples that reacted positively with each of the enzymes.

Table 1

Reactivity of proteins to SDAs and NSDAs

Enzyme	Patients (n=8)	Controls (n=8)
	Positive	Positive
G-3-P-Dehydrogenase		
from **human**	7/8	1/8
from **pig**	8/8	1/8
from **chicken**	7/8	2/8
from **yeast**	6/8	1/8
from **bacillus subtilis**	1/8	2/8
Enolase		
from **Rabbit**	7/8	1/8

The above results showed that the proteins obtained in accordance with the invention may be useful in the diagnosis of schizophrenia in a tested individual but require that the sample obtained and tested from the individual will comprise of prepared platelet-derived autoantibodies. The enzymes are not suitable for detecting schizophrenia directly in a plasma sample.

EXAMPLE 2: Identification of the epitope in the digested proteins capable of specific binding to SDAs:

Chemical (CNBr) and enzymatic digestions (Clostrapain) of human G-3-P-Dehydrogenase and rabbit Enolase were used to identify the epitope. Only the enzymatic digest of the Enolase revealed one peptide which was immunologically active (amino acids 372-399; The peptide having Seq. I.D. No. 1 in the following Table 2), i.e. was capable of binding SDAs to a higher extent and its capability of binding to NSDAs.

Based on the sequence of the epitope identified in the digested proteins, a number of peptides were synthesized by the method described in 1.8 above. The synthesized peptides were then evaluated for their binding activity to SDAs as compared to NSDAs as described above.

As seen in Table 2 below, several of the synthesized peptides showed a substantially higher binding activity to SDAs as compared to their binding to NSDAs (indicated as **YES** in the table) while others showed no significant differences in their binding to samples from schizophrenic and non-schizophrenic individuals (designed as **no** in the table).

Table 2

Peptide		Seq. I.D.No.	Activity
SGETEDTFIADLVVGLCTGQIKTGAPCR	(28aa)	1	YES
LVVGLCTCQUKTGPAC	(17aa)	2	YES
IADLVVGLCTGQIKTGAPCR	(20aa)	3	YES
ADLVVGLCTGQIKTGAPCR	(19aa)	4	YES
DLVVGLCTGQIKTGAPCR	(18aa)	5	YES
LVVGLCTGQIKTGAPCR	(17aa)	6	YES
LVVGLCTGQUKTGPACR	(17aa)	7	YES
LVVGLCTPQUKTGPACR	(17aa)	8	YES
SGETEDTFIADLVVGLCTGQ	(20aa)	9	No
VVGLCTGQIKTGAPCR	(16aa)	10	No
CTGQIKTGAPCR	(12aa)	11	No
LVVGLCTGQIKTGAPC	(16aa)	12	No
LVVGLCTGQIKTGAP	(15aa)	13	No
LVVGLCTGQIKTGPAC	(16aa)	14	No

Of the synthesized peptides, Peptide Seq. I.D. No. 2 was most capable of binding to antibodies found in high levels in schizophrenic patients.

EXAMPLE 3: Characterization of Peptide Seq. I.D. No. 2

Laser desorption mass spectroscopy of Peptide Seq. I.D. No. 2 (comprising three cysteins) directly after synthesis shows the presence of a monomer without a ring formation via the cysteins. However, after dissolving the peptide (about 4 mg) in 1 ml water/DMF/DMSO (1:1:1;v:v:v) and leaving the solution overnight at room temperature, the peptide forms a ring via two cysteins and a dimer via the remaining free cystein. No higher polymers could be detected. When testing the binding activity of the two forms of the peptide

to SDA, it became clear that the dimer form of the peptide was much more active in binding SDAs than the non-dimer form.

Chemical analysis of the peptide by reduction, e.g. by mercaptoethanol or sodium borohydrid, destroyed the immunological activity completely, whereas oxidation, e.g. air or oxygen, restored the immunological activity.

EXAMPLE 4: Binding activity of Peptide Seq. I.D. No. 2 to samples from schizophrenic and non-schizophrenic individuals:

The binding activity of Peptide 14 (Seq. I.D. No. 2) to isolated PAAs was tested using the method described above. As seen in Fig. 1A, the above peptide positively bound seven out of eight PAAs obtained from different schizophrenic patients. Fig. 1B shows that the above peptide did not bind PAAs obtained from eight different non-schizophrenic individuals. Peptide Seq. I.D. No. 9 was used as a negative control.

The capability of Peptide 14 (Seq. I.D. No. 2) to bind SDA in plasma samples obtained from schizophrenic patients was then tested. As seen in Fig. 2A, this peptide positively bound four out of five SDA from different schizophrenic patients. Fig. 2B shows that the above peptide did not bind NSDA from fourteen out of fifteen different non-schizophrenic individuals. Peptide 14 (Seq. I.D. No. 9) was used as a negative control.

EXAMPLE 5: Three dimensional structure:

The three-dimensional structure of the antigenic epitope of peptides according to the invention was predicted using a computerized program based on the mineral energy calculations.

As seen in Fig. 3, the predicted structure of the antigenic epitope is a cyclic structure comprising a hydrophobic core and an extension comprising about two positive charges. The positive charged extensions may be positioned in one of many possible spatial orientations.

EXAMPLE 6: Scanning of the surface of the enolase to find epitopes matching the calculated epitopes of the peptides:

The water model three-dimensional structure of the peptides of the invention was calculated. An x-ray three-dimensional structure of enolase generated from a public peptide database was then scanned and the position of the amino acids of the peptides of the invention was compared to the position of the amino acids of the enolase surface to see if an epitope which matches one or more of the calculated epitopes of the peptides of the invention could be found on the surface of the enolase.

As seen in Fig. 4 which is a computer simulation of the scanning of the surface of the enolase, an epitope was found on the surface of the enolase which is comprised of a cluster of hydrophobic amino acids (Leucine, Alanine and Proline) surrounded by positive charged amino acids (Arginine and Hystidine) which matches the epitope simulated from the peptides of the invention. Thus, the predicted structure of the antigenic epitope of the peptides of the invention could indeed be found on the cell surface of enolase.

CLAIMS:

1. A peptide which binds antibodies that are found in elevated levels in body fluids of schizophrenic patients.

2. A peptide according to claim 1, which binds antibodies that are capable of specific binding to a peptide having the amino acid sequence of Seq. I.D. No. 2.

3. A peptide according to claim 1 or 2, which binds antibodies that are capable of binding to a peptide selected from the group. consisting of:

i. SGETEDTFIADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 1)
ii. LVVGLCTCQIKTGPAC (Seq. I.D. No. 2)
iii. IADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 3)
iv. ADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 4)
v. DLVVGLCTGQIKTGAPCR (Seq. I.D. No. 5)
vi. LVVGLCTGQIKTGAPCR (Seq. I.D. No. 6)
vii. LVVGLCTGQIKTGPACR (Seq. I.D. No. 7)
viii. LVVGLCTPQIKTGPACR (Seq. I.D. No. 8)

4. A peptide according to any one of claims 1-3, capable of binding to antibodies which do not bind to peptides selected from the group consisting of:

i. SGETEDTFIADLVVGLCTGQ (Seq. I.D. No. 9)
ii. VVGLCTGQIKTGAPCR (Seq. I.D. No. 10)
iii. CTGQIKTGAPCR (Seq. I.D. No. 11)
iv. LVVGLCTGQIKTGAPC (Seq. ID. No. 12)
v. LVVGLCTGQIKTGAP (S eq. ID No. 13)
vi. LVVGLCTGQIKTGPAC (Seq. ID No. 14)

5. A peptide according to any one of claims 1-4, comprising an amino acid sequence selected from the group, consisting of:

i. SGETEDTFIADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 1)
ii. LVVGLCTCQIKTGPAC (Seq. I.D. No. 2)
iii. IADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 3)
iv. ADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 4)
v. DLVVGLCTGQIKTGAPCR (Seq. I.D. No. 5)
vi. LVVGLCTGQIKTGAPCR (Seq. I.D. No. 6)
vii. LVVGLCTGQIKTGPACR (Seq. I.D. No. 7)
viii. LVVGLCTPQIKTGPACR (Seq. I.D. No. 8).

6. A peptide according to any one of claims 1-4, selected from the group consisting of:

i. SGETEDTFIADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 1)
ii. LVVGLCTCQIKTGPAC (Seq. I.D. No. 2)
iii. IADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 3)
iv. ADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 4)
v. DLVVGLCTGQIKTGAPCR (Seq. I.D. No. 5)
vi. LVVGLCTGQIKTGAPCR (Seq. I.D. No. 6)
vii. LVVGLCTGQIKTGPACR (Seq. I.D. No. 7)
viii. LVVGLCTPQIKTGPACR (Seq. I.D. No. 8)

7. A peptide which binds antibodies that are found in elevated levels in body fluids of schizophrenic patients, said peptide comprising at least one antigenic epitope, said epitope having a cylic three dimenional structure consisting a hydrophobic core and a positively charged extension.

8. An assay for the diagnosis of schizophrenia in an individual, comprising the following steps:

(a) obtaining a sample from said individual being a blood sample, a platelet-containing fraction thereof, or a fraction containing platelet-associated antibodies (PAA) shed from the platelets;

(b) contacting said sample with a peptide capable of binding to antibodies that are found in elevated levels in body fluids of schizophrenic patients.

(c) determining the level of binding of said peptide to said sample, a level higher than the binding level of said peptide to a sample from non-schizophrenic individuals indicating that said individual has a high likelihood of having schizophrenia.

9. An assay in accordance with claim 8, wherein the peptide of step (b) is a peptide having the amino acid sequence of Seq.ID.No.2

10. An assay in accordance with claim 8, wherein the peptide in step (b) comprises an a.a. sequence selected from the group consisting of:

i. SGETEDTFIADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 1)
ii. LVVGLCTCQIKTGPAC (Seq. I.D. No. 2)
iii. IADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 3)
iv. ADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 4)
v. DLVVGLCTGQIKTGAPCR (Seq. I.D. No. 5)
vi. LVVGLCTGQIKTGAPCR (Seq. I.D. No. 6)
vii. LVVGLCTGQIKTGPACR (Seq. I.D. No. 7)
viii. LVVGLCTPQIKTGPACR (Seq. I.D. No. 8).

11. An assay according to claim 8, wherin the peptide in step (b) is a peptide selected from the group consisting of:

i. SGETEDTFIADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 1)
ii. LVVGLCTCQIKTGPAC (Seq. I.D. No. 2)

iii. IADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 3)

iv. ADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 4)

v. DLVVGLCTGQIKTGAPCR (Seq. I.D. No. 5)

vi. LVVGLCTGQIKTGAPCR (Seq. I.D. No. 6)

vii. LVVGLCTGQIKTGPACR (Seq. I.D. No. 7)

viii. LVVGLCTPQIKTGPACR (Seq. I.D. No. 8)

12. An assay in accordance with Claim 8, wherein the peptide in step (b) is a peptide in accordance with claim 7.

13. An assay in accordance with any of Claims 8-12, wherein said sample obtained from the individual is a whole blood sample.

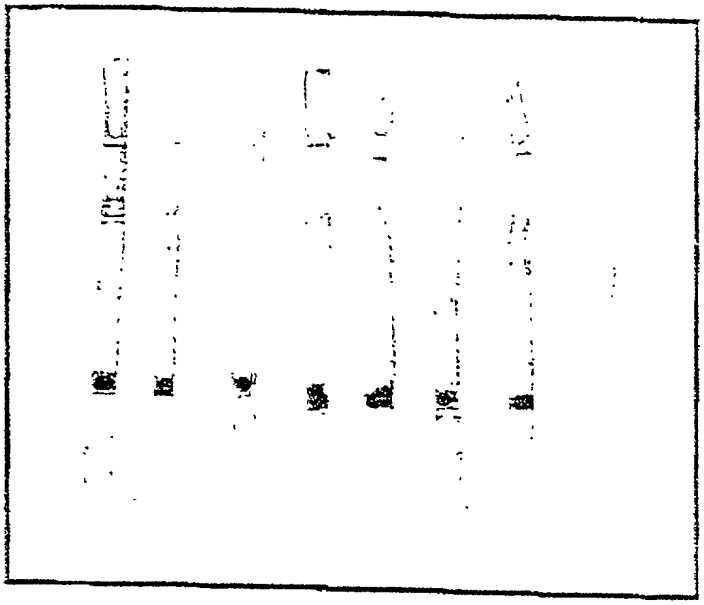
14. A kit for use in the diagnosis of schizophrenia comprising:

i. a support comprising one or more peptides in accordance with any one of claims 1-7 immobilized onto it;

ii. an anti-human immunoglobulin antibody or fragment thereof conjugated to a detectable marker;

iii. reagents required for carrying out the assay, and;

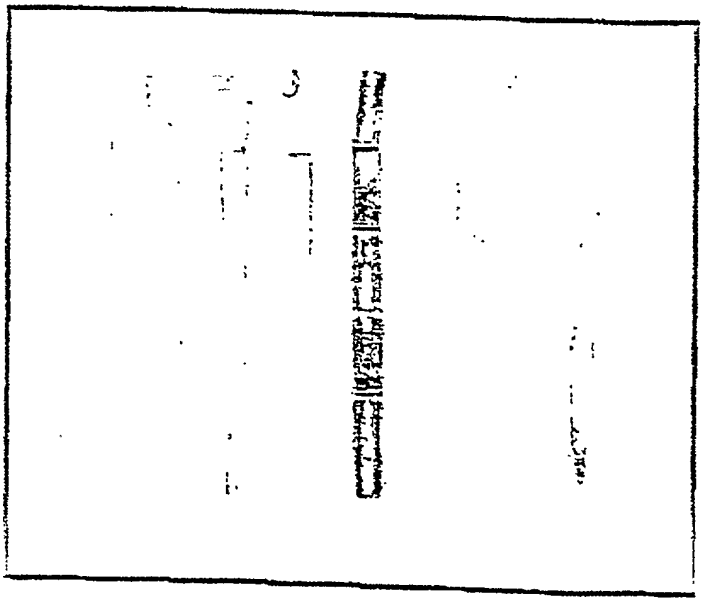
iv. instructions for use.



CONTROL

PEPTIDE 14

FIG.1A



CONTROL

PEPTIDE 14

FIG.1B

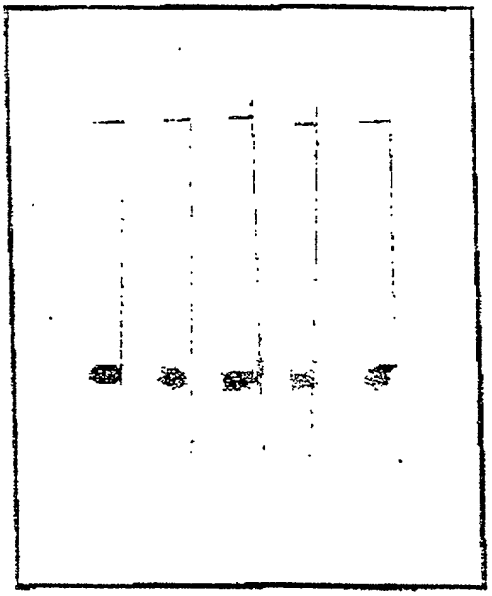


FIG.2A

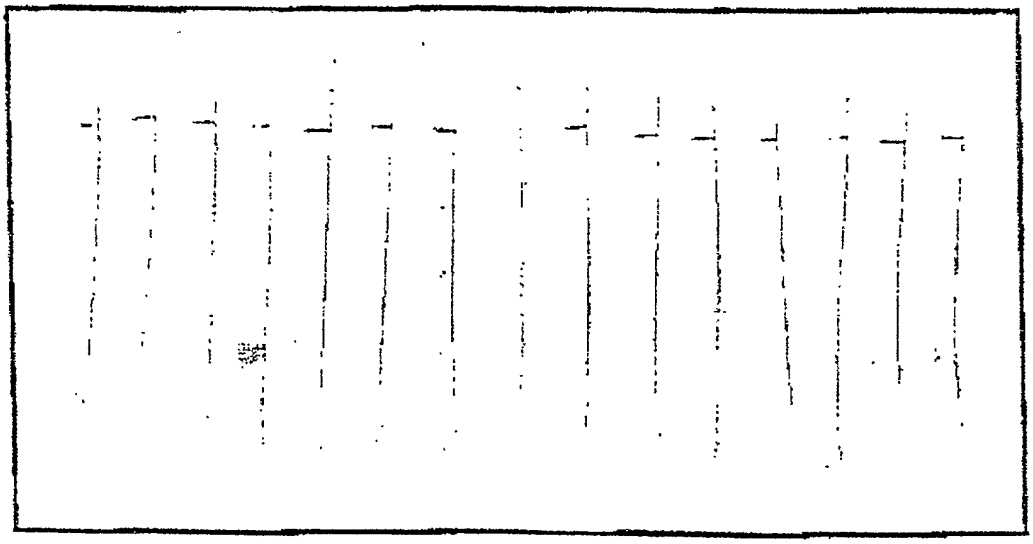


FIG.2B

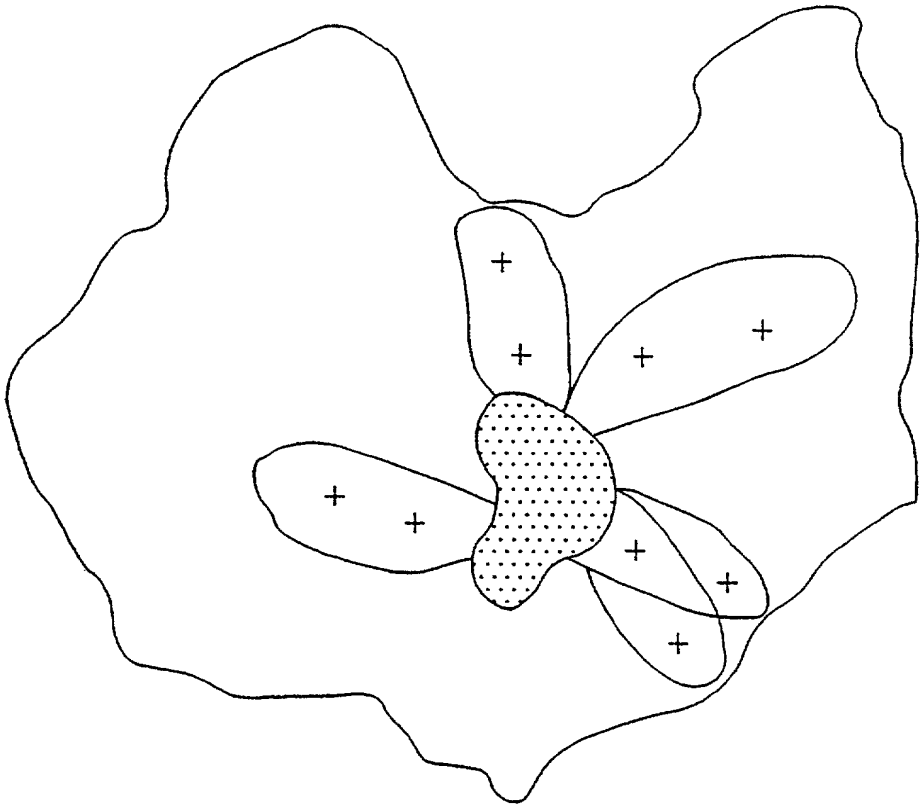


FIG.3

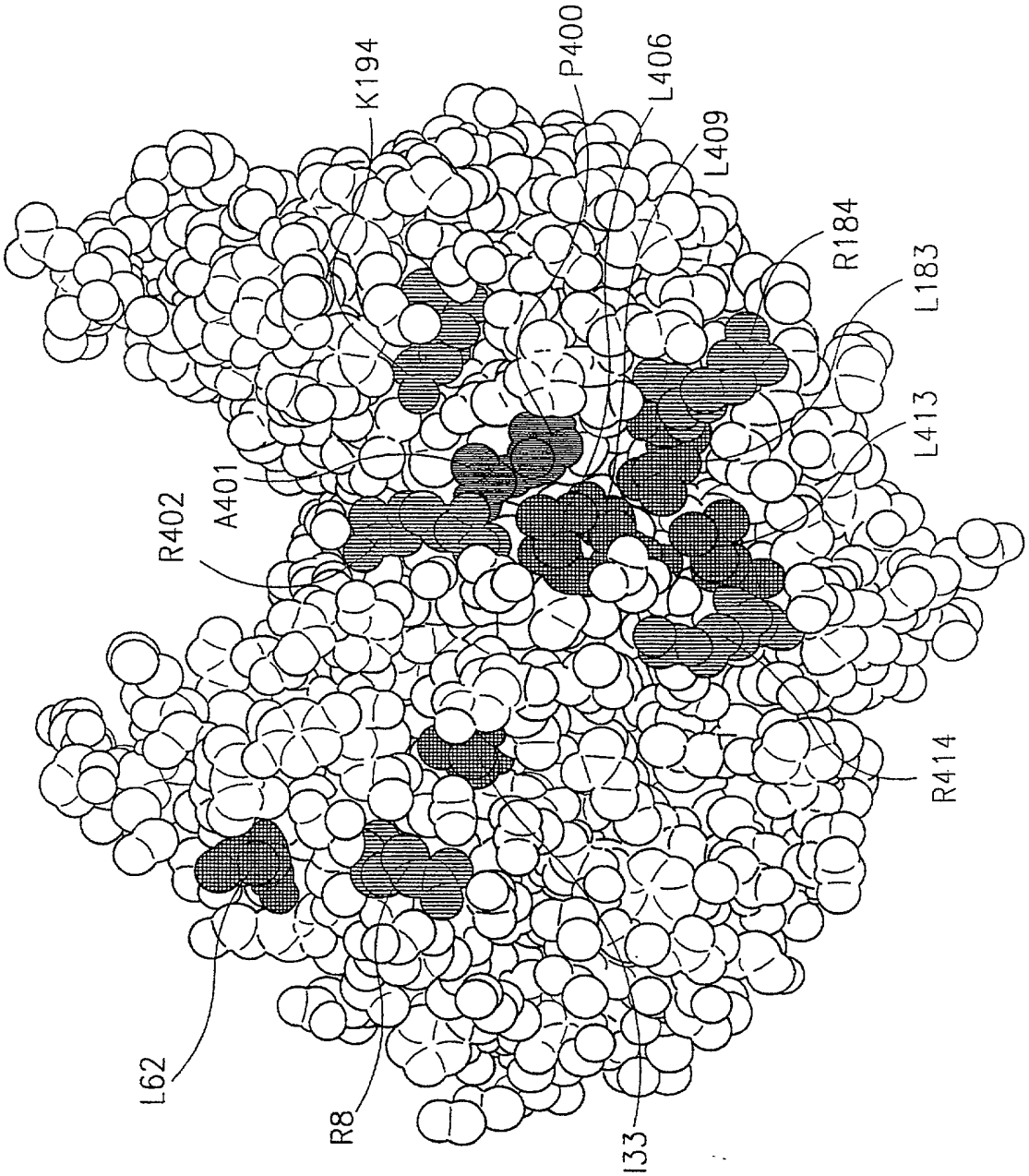


FIG.4

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT:
(A) NAME: YEDA RESEARCH AND DEVELOPMENT COMPANY LTD.
(B) STREET: THE WEIZMANN INSTITUTE OF SCIENCE
(C) CITY: REHOVOT
(E) COUNTRY: ISRAEL
(F) POSTAL CODE (ZIP): P.O.BOX 95
(G) TELEPHONE: +08 9470617
(H) TELEFAX: +08 9470739

(ii) TITLE OF INVENTION: ASSAY FOR THE DIAGNOSIS OF SCHIZOPHRENIA BASED ON A NEW PEPTIDE

(iii) NUMBER OF SEQUENCES: 14

(iv) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30 (EPO)

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

Ser Gly Glu Thr Glu Asp Thr Phe Ile Ala Asp Leu Val Val Gly Leu
1 5 10 15

Cys Thr Gly Gln Ile Lys Thr Gly Ala Pro Cys Arg
20 25

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

Leu Val Val Gly Leu Cys Thr Cys Gln Ile Lys Thr Gly Pro Ala Cys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

Ile Ala Asp Leu Val Val Gly Leu Cys Thr Gly Gln Ile Lys Thr Gly
1 5 10 15

Ala Pro Cys Arg
20

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

Ala Asp Leu Val Val Gly Leu Cys Thr Gly Gln Ile Lys Thr Gly Ala
1 5 10 15

Pro Cys Arg

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

Asp Leu Val Val Gly Leu Cys Thr Gly Gln Ile Lys Thr Gly Ala Pro
1 5 10 15

Cys Arg

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

Leu Val Val Gly Leu Cys Thr Gly Gln Ile Lys Thr Gly Ala Pro Cys
1 5 10 15

Arg

(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

Leu Val Val Gly Leu Cys Thr Gly Gln Ile Lys Thr Gly Pro Ala Cys
1 5 10 15

Arg

(2) INFORMATION FOR SEQ ID NO: 8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

Leu Val Val Gly Leu Cys Thr Pro Gln Ile Lys Thr Gly Pro Ala Cys
1 5 10 15

Arg

(2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids

(B) TYPE: amino acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

Ser Gly Glu Thr Glu Asp Thr Phe Ile Ala Asp Leu Val Val Gly Leu
1 5 10 15

Cys Thr Gly Gln
20

(2) INFORMATION FOR SEQ ID NO: 10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

Val Val Gly Leu Cys Thr Gly Gln Ile Lys Thr Gly Ala Pro Cys Arg
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

Cys Thr Gly Gln Ile Lys Thr Gly Ala Pro Cys Arg
1 5 10

(2) INFORMATION FOR SEQ ID NO: 12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

Leu Val Val Gly Leu Cys Thr Gly Gln Ile Lys Thr Gly Ala Pro Cys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

Leu Val Val Gly Leu Cys Thr Gly Gln Ile Lys Thr Gly Ala Pro
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

Leu	Val	Val	Gly	Leu	Cys	Thr	Gly	Gln	Ile	Lys	Thr	Gly	Pro	Ala	Cys
1				5					10					15	

DECLARATION FOR PATENT APPLICATION	Attorney Docket: 24390 Page 1 of 7

As a below-named inventor(s), I/we hereby declare that:

My/Our residence(s), post office address(es) and citizenship(s) is/are as stated below next to my/our name(s).

I/We believe I/we am/are the original inventor, first and sole (*if only one name is listed below*) or the original, first and joint inventors (*if plural names are listed below*) of the subject matter which is claimed, and for which a patent is sought on the invention entitled:

ASSAY FOR THE DIAGNOSIS OF SCHIZOPHRENIA BASED ON A NEW PEPTIDE

the specification of which: (check one)

[ ] is attached hereto.

[X] was filed on 30 March 1999 as Serial No. PCT/IL99/00190
29 September 2000 09/647,457
and was amended on _____ (if applicable).

We hereby state that we have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We acknowledge the duty to disclose information which is material to the patentability of this application as defined by 37 CFR § 1.56.

We hereby claim foreign priority benefits under 35 U.S.C. § 119 of any foreign application(s) for patent or inventor's certificate listed below, and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Applications:

			Priority Claimed	
123825 (Application No.)	IL (Country)	02 /April / 1998 (Day/Month/Year Filed)	(X) Yes	[ ] No
_____ (Application No.)	_____ (Country)	/ / (Day/Month/Year Filed)	[ ] Yes	[ ] No
_____ (Application No.)	_____ (Country)	/ / (Day/Month/Year Filed)	[ ] Yes	[ ] No

We hereby appoint Gary M. Nath, Reg. No. 26,965; Harold L. Novick, Reg. No. 26,011; Todd L. Juneau, Reg. No. 40,669; Lee C. Heiman, Reg. No. 41,827; Jerald L. Meyer, Reg. No. 41,194; Joshua B. Goldberg, Reg. No. 44,126; David R. Murphy, Reg. No. 22,751; Paul A. Sanker, Reg. No. 43,418; Deborah U. Yellin, 45,904; Nahied K. Usman, Reg. No. 47,108; and Roger Kahn, Reg. No. 46,376; all my attorneys to prosecute this application and transact all business in the U.S. Patent and Trademark Office connected therewith.

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020529
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We hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by 35 U.S.C. § 112, first paragraph, I/we acknowledge the duty to disclose material information as defined in 37 CFR § 1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(U.S. Application Serial No.) (U.S. Filing Date) (Status--patented, pending, abandoned)

(U.S. Application Serial No.) (U.S. Filing Date) (Status--patented, pending, abandoned)

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DECLARATION FOR PATENT APPLICATION	Attorney Docket: 24390 Page 2 of 2

We hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Inventor's Signature [signature] Date 20/11/2000

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DECLARATION FOR PATENT APPLICATION	Attorney Docket: 24200 Page 2 of 2

We hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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2-00